REMARKS

Claims 1, 4-11, 15-21, 56-60 and 63-68 are pending and stand rejected in this application. Claims 1, 63 and 65 have been amended, and new claims 69-71 have been added herein. No new matter has been added by way of this amendment, and support can be found throughout the specification, *e.g.*, at page 17, lines 26-31, and original claims 43-44. Following entry of this amendment, claims 1, 4-11, 15-21, 56-60, and 63-71 will be pending in this application. Applicants respectfully request reconsideration of pending claims 1, 4-11, 15-21, 56-60, and 63-71.

The specification has also been amended herein to indicate that this application is a divisional application of U.S. Patent Application Serial No. 09/419,114 ("the '114 application"). Applicants note that in the Restriction Requirement dated July 3, 2001, the Examiner restricted claims in the parent '114 application into three groups which included 1) microspheres comprising crosslinked polyvinyl alcohol; 2) a method for prophylactic or therapeutic embolization, and 3) a process for producing crosslinked polyvinyl alcohol microspheres. In a Response dated August 29, 2001, the Applicants chose to pursue the Group 2 "method" claims in the '114 application. The Group 1 "microsphere" claims are now being pursued in the instant application. As such, the instant application is properly deemed a divisional application of the '114 application.

A Supplemental IDS is submitted herewith, which includes papers related to the Opposition of counterpart European Patent No. EP 1128816 B1. Applicants request that these documents be considered by the Examiner and be made of record in the present application, and that an initialed copy of the List of References Cited by Applicant be returned in accordance with MPEP § 609.

I. Rejection Under 35 U.S.C. § 103

A number of rejections under 35 U.S.C. § 103 have been maintained by the Examiner. In order to fully address the Examiner's concerns, each ground of rejection will be discussed individually below.

It is noted, as the outset, that *KSR International Co. v. Teleflex Inc.*, No. 04-1350, 550 U.S. __ (2007), the references cited by the Examiner provided the patentee with all the elements of the claimed invention— the claimed invention was obtained merely by combining the references "like

pieces of a puzzle." *KSR, slip op.*, pp. 16-17. However, the instant case is distinguishable because the references cited by the Examiner, either individually or in combination, do not provide each element of the instant claims as discussed in more detail below.

A. Bachtsi

Claims 1, 4-6, 11, 15-18 and 56-60 remain rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Bachtsi *et al.* (1995) *J. Microencapsulation,* 12:23-25 ("Bachtsi") (Office Action, page 3).

Applicants respectfully traverse this ground of rejection, for essentially the reasons of record.

The U.S. Supreme Court has recently addressed the test for obviousness under 35 U.S.C. § 103. *KSR International Co. v. Teleflex Inc.*, No. 04-1350, 550 U.S. __ (2007). In *KSR,* the Supreme Court rejected the Federal Circuit's *rigid application* of the 'teaching, suggestion, motivation" test ("the TSM test") in determining obviousness in the particular case in question. *Id., slip op.* p. 11. According to the Supreme Court, the correct standard to apply is set forth in *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1 (1966). *Id., slip op.* p. 2. However, the *KSR* decision indicated that while the TSM test is not the sole method for determining obviousness, it may still be a factor. *Id. slip op.* p. 14 ("When it first established [the TSM test], the Court...captured a helpful insight."). Indeed, on May 3, 2007, the Deputy Commissioner of Patents circulated a memorandum to the Technology Center Directors ("USPTO Memorandum") pointing out that the TSM test was not completely abolished in *KSR*.

The *Graham* factual inquiries, which establish a guide for determining obviousness, are: (1) determine the scope and contents of the prior art; (2) ascertain the differences between the prior art and the claims at issue; (3) resolve the level of ordinary skill in the pertinent art; and (4) evaluate any evidence of secondary considerations. *KSR, slip op.* p. 2 (*citing Graham,* 383 U.S. at 15-17).

The instant claims are not obvious because the microspheres disclosed in Bachtsi differ from microspheres recited in the instant claims. Furthermore, the scope and content of

Bachtsi does not provide a reason that would have prompted one of ordinary skill in the art to modify the teachings of Bachtsi to arrive at the methods of the instant claims.

In the prior Office Action dated October 30, 2006, the Examiner, in an attempt to support the rejection, cites the particle preparation steps disclosed in Bachtsi:

> The dehydrated particles were subsequently suspended in a NaOH buffer solution (pH 8-9) overnight to remove any unreacted chemicals. The crosslinked particles were then washed several times with distilled water until the pH of the washing medium reached a value of 7)...Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the invention of Bachtsi et al. and generate sterile microspheres crosslinked PVA [*sic*]...wherein the aldehydes on the microspheres are neutralized because Bachtsi et al. disclose crosslinked PVA microspheres that meet the limitations of the instant invention...The neutralized aldehydes attached to the microspheres are obvious because based on the procedure of generating the microspheres of the prior art, Bachtsi et al. disclose that the particles were suspended in NaOH buffer and washed several timed with distilled water such that a neutral pH was obtained. As a result, a skilled practitioner in the art would recognize that NaOH acts as a neutralizing agent.

(page 4, emphasis in text).

Respectfully, Applicants once again submit that the Examiner may be misunderstanding the rationale for Bachtsi's use of NaOH. Bachtsi states that the NaOH buffer solution (pH 8-9) is used to "remove any unreacted chemicals" (Bachtsi, page 25). For example, skilled artisans will appreciate that organic acids are a byproduct of the glutaraldehyde crosslinking reaction (see Bachtsi, page 25), requiring washing and (pH) neutralization in later steps. In addition, acetic acid and sulfuric acid are also used in the formation of the particles (*Id.*). That is, the NaOH buffer was added as a high pH wash solution to assist in the removal of excess chemicals such as acetic acid or sulfuric acid, organic acid side products, or other side products or excess chemicals remaining after the previous reaction steps.

Distilled water was then used in Bachtsi as a secondary wash solution to wash the microspheres and to reduce the pH to 7 (a neutral pH), after being at a basic pH 8-9 (*Id.*). That is, NaOH and distilled water were used to wash the excess leftover chemicals from the

microspheres, rather than to chemically neutralize the aldehyde groups that are present on the microspheres, as recited in the claimed invention (for support, see also page 27 of Bachtsi).

The Examiner has provided no evidence to indicate that the reaction steps described in the Bachtsi reference are such that would result in presently claimed microspheres, or that addition of a simple NaOH wash buffer to unreacted aldehydes would chemically react as required to neutralize aldehydes as presently claimed (Applicants maintain that there is none). Bachtsi only uses sulphuric acid, PVA and glutaraldehyde, unlike the reactants used in the instant case.

To supplement Bachtsi, the Examiner newly cites US 6,242,512 by Figge *et al.* ("Figge") (Office Action, pages 5-6). The Examiner states that Figge demonstrates that NaOH is a neutralizing agent that may be used with polyvinyl alcohols. However, Applicants once again point out that, as in Bachtsi, the NaOH used in Figge is added to adjust the pH to a desired range, and not to neutralize the aldehydes on the microspheres, as is the case in the claimed instant invention.

In contrast to Bachtsi and Figge's use of NaOH, the present specification exemplifies chemical reaction conditions that chemically neutralize aldehydes. For instance, the Examples in the specification use a "Tris-HCl" buffer. As those skilled in the art will appreciate, "Tris" is tris(hydroxymethyl)-aminomethane, a well known organic molecule having a primary amino group, which reacts unambiguously with aldehyde groups that are still present on the surface of the beads. In addition to Tris, other amino alcohols having a primary amino group disclosed in the specification are 2-aminoethanol, aminosorbitol and glucosamine (see, for example, originally filed claims 43 and 44 and page 17, lines 26-31 in the specification as filed).

Further, Applicants respectfully submit that both Bachtsi and Figge are in non-analogous fields. As the Examiner is aware, "[i]n order to rely on a reference as a basis for rejection of an applicant's invention, the reference must either be in the field of applicant's endeavor or, if not, then be reasonably pertinent to the particular problem with which the inventor was concerned." *In re Oetiker*, 977 F.2d 1443, 1446 (Fed. Cir. 1992). *See also In re Clay*, 966 F.2d 656, 659 (Fed. Cir. 1992). The focus of Bachtsi is on methods of altering enzyme release rates. This is in the field of pharmaceutical drug delivery, which is a

completely different field than the field of embolization. Thus, it would be highly unlikely for one of skill in the art to even find this reference, much less read it and be able to modify its principles to prepare the claimed compositions. Additionally, the focus of Figge is the preparation of polymer powders that are used for bonding agents in adhesives, plasters, or paints (see abstract). This is also in a completely different field than the field of the instant invention, and would not have been likely to be read by one of skill in the art of embolization.

In view of the above, Applicants submit that the present claims are non-obvious over the disclosure of Bachtsi. Accordingly, reconsideration and withdrawal of this ground of rejection is respectfully requested.

B. Bachtsi in View of Tarara (claims 1, 4, 5, 8-11, 15-17, 19-21, 56-60 and 63-68)

The Examiner has rejected claims 1, 4, 5, 8-11, 15-17, 19-21, 56-60 and 63-68 under 35 U.S.C. § 103(a) as allegedly unpatentable over Bachtsi in view of Tarara *et al.* (U.S. Patent No. 6,565,885) ("Tarara") (Office Action, pg. 3).

Applicants respectfully traverse this round of rejection.

In *KSR*, the Supreme Court emphasized that the "combination of familiar elements according to known methods is likely to be obvious when it yields no more than predictable results." *KSR, slip op.* p. 12. However, the Court cautioned that "[f]ollowing these principles may be more difficult in other cases...because the claimed subject matter may involve more than the simple substitution of one known element for another...." *Id., slip op.* p. 14. Further, "it can be important to *identify a reason* that would have prompted a person of ordinary skill...to combine the elements in the way the claimed new invention does." *Id., slip op.* p. 15 (emphasis added); *see also* USPTO Memorandum ("it remains necessary to identify the reason why a person of ordinary skill in the art would have combined the prior art elements in the manner claimed.").

The instant claims are not obvious because the microspheres disclosed in Bachtsi in view of Tarara differ from microspheres recited in the instant claims. Furthermore, the scope and content of these references does not provide a reason that would have prompted one of

ordinary skill in the art to modify the teachings of Bachtsi in view of Tarara to arrive at the methods of the instant claims.

As established above, the instant case involves more than the "simple substitution" of known elements in the prior art. Therefore, the Examiner must provide a reason why one of ordinary skill in the art would use the teachings of combined teachings of Bachtsi and Tarara--which are in completely different fields of technology--and somehow arrive at the microspheres and injectable compositions of the instant claims. The Examiner merely relies on the alleged overlap of certain, specific, "cherry-picked" elements of the microspheres of the cited references with those of the instant claims (Office Action, paged 3-7). However, the Examiner has provided no basis for the allegation that the instant claims are obvious over these references, and the Examiner's burden to support a rejection on the grounds of obviousness with explicit, articulate reasoning remains. *KSR, slip op.* p. 14 (*citing In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006); *see also* USPTO Memorandum.

In *KSR,* the references cited by the Examiner provided the patentee with all the elements of the claimed invention— the claimed invention was obtained merely by combining the references "like pieces of a puzzle." *KSR, slip op.*, pp. 16-17. However, the instant case is distinguishable because Bachtsi and Tarara, either individually or in combination, do not provide each element of the instant claims, namely, *any* microspheres that are sterile and comprise cross-linked PVA, *much less* microspheres comprising crosslinked polyvinylalcohol, wherein said microspheres (a) have a diameter ranging from about 10 μm to about 2,000 μm, (b) are substantially spherical, (c) are substantially uniform in size and shape, (d) are sterile, and further comprise (e) a marking agent (*e.g.,* claims 63-64 and 66-67) or anti-angiogenic agent (*e.g.,* claims 65 and 68).

Therefore, because Bachtsi and Tarara, either individually or in combination, do not disclose the microspheres or injectable compositions of the instant claims, and because substantial differences exist between the instant claims and the scope and content of Bachtsi and Tarara as discussed above, the instant claims are not obvious over this combination of references.

Further, the teachings of Bachtsi and Tarara, either individually or in combination, would not prompt a person of ordinary skill to combine the elements to arrive at the instant claims.

Applicants further note that the invention as a whole must be considered when determining obviousness, rather than the obviousness of any substitution of modification. *Hybritech v. Monoclonal Antibodies, Inc.*, 231 USPQ 81 (Fed. Cir. 1986).

Respectfully, Applicants submit that the Examiner is using impermissible hindsight to "pick and choose" various elements from throughout the extensive specification of Tarara, while using the instant claims as a roadmap, instead of appreciating Applicants' invention as a whole. That being said, the Examiner has also failed to point to any text in the specification related to sterile, cross-linked PVA microspheres useful in embolization, or suspensions thereof. Indeed, Applicants submit that *nowhere* does Tarara disclose or suggest *any* sterile and/or cross-linked PVA particles, much less sterile, crosslinked PVA microspheres having the very specific combination of elements as recited in the claims. In addition, Tarara fails to disclose or suggest microspheres, wherein the aldehydes on the microspheres are neutralized.

The Examiner further opines that a skilled practitioner would be motivated to utilize the teachings of Tarara because Tarara is directed to microspheres which may optionally comprise PVA (Office Action, page 6). However, Applicants respectfully maintain that, because the Tarara reference is in the field of powders for nasal administration, one of skill in the art would not consider applying Tarara's teachings towards the preparation of the claimed compositions of the instant invention for embolization. As mentioned above, "[i]n order to rely on a reference as a basis for rejection of an applicant's invention, the reference must either be in the field of applicant's endeavor or, if not, then be reasonably pertinent to the particular problem with which the inventor was concerned." *In re Oetiker*, 977 F.2d 1443, 1446 (Fed. Cir. 1992). However, Applicants submit that Tarara is neither in the field of Applicants'' endeavor nor pertinent to the particular problem with which the inventor was concerned.

The claims are related to microspheres useful in the embolization of blood vessels; whereas, Tarara is related to spray drying methods for forming powder compositions for nasal or pulmonary administration, as well as non-pharmaceutical uses for industrial products, such as spray paint:

> Accordingly, it is an object of the present invention to provide methods and preparations that advantageously allow for the nasal or pulmonary administration of powders having relatively high

> fine particle fractions. It is a further object of the present invention to provide stabilized preparations suitable for aerosolization and subsequent administration to the pulmonary air passages of a patient in need thereof. It is yet another object of the present invention to provide powders that may be used to provide stabilized dispersions. It is still a further object of the present invention to provide powders exhibiting relatively low cohesive forces that are compatible for use in dry powder inhalers.

(Col. 3, lines 20-34; emphasis added).

> By way of contrast [to prior art formulations], the present invention uses methods and compositions that yield powder formulations having extraordinarily low bulk density, thereby reducing the minimal filling weight that is commercially feasible for use in dry powder inhalation devices. That is, most unit dose containers designed for DPIs are filled using fixed volume or gravimetric techniques. Contrary to prior art formulations, the present invention provides powders wherein the active or bioactive agent and the incipients or bulking agents make-up the entire inhaled particle.

(Col. 9, lines 9-12; emphasis added). Tarara further states that:

> The present invention offers benefits over prior art preparations for use in application which require aerosolization or atomization. In such non-pharmaceutical uses the preparations can be in the form of a liquid suspension (such as with a propellant) or as a dry powder. Preferred embodiments comprising perforated microstructures as described herein include, but are not limited to, ink jet printing formulations, powder coating, spray paint, spray pesticides, etc.

(Col. 45, lines 2-10; emphasis added).

Given the above disclosure of Tarara, it can be said that that reference teaches away from injectable formulations as its focus is clearly inhalation. If the Examiner does not agree, it must be admitted that there is little evidence that inhalation technology can be applied to injectables much less an indication that the ordinary skilled artisan would do so.

Accordingly, for at least these reasons, Applicants submit that the ordinary skilled artisan would not look to Tarara with respect to the art of embolization and/or to overcome the deficiencies of Bachtsi, as discussed below.

Thus, Applicants respectfully assert that at least independent claims 1, 11, 63, 65, 66 and 68 are non-obvious over Tarara. In addition, dependent claims 4-10, 15-21, 56-60, 64, and 67 (as well as new claims 69-71) are also non-obvious over Tarara (see, *e.g., In re Fine*, 837 F.2d 1071 (Fed. Cir. 1988) (If an independent claim is nonobvious under 35 U.S.C. § 103, then any claim depending therefrom is nonobvious). Accordingly, reconsideration and withdrawal of this ground of rejection is respectfully requested.

C. Bachtsi in View of Tarara[1] (claims 1, 4-6, 11, 15-18, 56-60 and 63-68)

The Examiner has maintained the rejection of claims 1, 4-6, 11, 15-18, 56-60 and 63-68 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Bachtsi in view of Tarara (Office Action, page 2).

Applicants respectfully traverse this ground of rejection.

Both Bachtsi and Tarara are discussed in detail above, and the arguments are equally applicable with respect to the combination of references.

As mentioned above, the instant claims are not obvious because the microspheres disclosed in Bachtsi in view of Tarara differ from microspheres recited in the instant claims. Furthermore, the scope and content of these references does not provide a reason that would have prompted one of ordinary skill in the art to modify the teachings of Bachtsi in view of Tarara to arrive at the methods of the instant claims.

For essentially the same reasons discussed above, Applicants maintain that neither Bachtsi or Tarara, either alone or in combination, disclose or suggest microspheres, wherein aldehydes on the microspheres are neutralized, as recited in claims 1, 4-11, 15-21, and 56-60. As such claims 1, 4-6, 11, 15-18, 56-60 are non-obvious over Bachtsi, either alone or in combination with Tarara.

Further, with respect to claims 63-68, Applicants submit that neither Bachtsi nor Tarara, either alone or in combination, disclose or suggest *any* microspheres that are sterile

[1] Applicants note that this combination of references was twice-cited by the Examiner in the Office Action regarding claims 1, 4, 5, 8-11, 15-17, 19-21, 56-60 and 63-68 (see I-B above) and again with respect to 1, 4-6, 11, 15-18, 56-60 and 63-68 (current section I-C). See also page 2 of the Office Action, Sections II and III, respectively. For the sake of completeness, each rejection is addressed individually herein.

and comprise cross-linked PVA, *much less* microspheres comprising crosslinked polyvinylalcohol as recited by the claims

In *KSR,* the references cited by the Examiner provided the patentee with all the elements of the claimed invention— the claimed invention was obtained merely by combining the references "like pieces of a puzzle." *KSR, slip op.,* pp. 16-17. However, the instant case is distinguishable because Bachtsi and Tarara, either individually or in combination, do not provide each element of the instant claims, namely, *any* microspheres that are sterile and comprise cross-linked PVA, *much less* microspheres comprising crosslinked polyvinylalcohol, wherein said microspheres (a) have a diameter ranging from about 10 μm to about 2,000 μm, (b) are substantially spherical, (c) are substantially uniform in size and shape, (d) are sterile and further comprise (e) a marking agent (claims 63-64 and 66-67) or anti-angiogenic agent (claims 65 and 68).

Therefore, because Bachtsi and Tarara, either individually or in combination, do not disclose the microspheres or injectable compositions of the instant claims, and because substantial differences exist between the instant claims and the scope and content of Bachtsi and Tarara as discussed above, the instant claims are not obvious over this combination of references.

Further, the teachings of Bachtsi and Tarara, either individually or in combination, would not prompt a person of ordinary skill to combine the elements to arrive at the instant claims.

In *KSR*, the Supreme Court emphasized that the "combination of familiar elements according to known methods is likely to be obvious when it yields no more than predictable results." *KSR, slip op.* p. 12. However, the Court cautioned that "[f]ollowing these principles may be more difficult in other cases...because the claimed subject matter may involve more than the simple substitution of one known element for another...." *Id., slip op.* p. 14. Further, "it can be important to *identify a reason* that would have prompted a person of ordinary skill...to combine the elements in the way the claimed new invention does." *Id., slip op.* p. 15 (emphasis added); *see also* USPTO Memorandum ("it remains necessary to identify the reason why a person of ordinary skill in the art would have combined the prior art elements in the manner claimed.").

As established above, the instant case involves more than the "simple substitution" of known elements in the prior art. Therefore, the Examiner must provide a reason why one of ordinary skill in the art would use the teachings of combined teachings of Bachtsi and Tarara--which are in completely different fields of technology--and somehow arrive at the microspheres and injectable compositions of the instant claims. The Examiner merely relies on the alleged overlap of certain, specific, "cherry-picked" elements of the microspheres of the cited references with those of the instant claims (Office Action, paged 3-7). However, the Examiner has provided no basis for the allegation that the instant claims are obvious over these references, and the Examiner's burden to support a rejection on the grounds of obviousness with explicit, articulate reasoning remains. *KSR*, *slip op.* p. 14 (*citing In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006); *see also* USPTO Memorandum.

The Examiner acknowledges that Bachtsi fails to disclose or suggest sterile microspheres (prior Office Action dated October 30, 2006, page 3) or various types of cell adhesion promoters, marking agents, and anti-angiogenic agents (prior Office Action dated October 30, 2006, page 7). In an attempt to supply the deficiency in the teachings of Bachtsi, the Examiner once again cites Tarara as teaching cell adhesion promoters, marking agents and anti-angiogenic agents (Office Action, page 6).

However, it would not have been obvious to modify the microspheres of Bachtsi with the marking agents and anti-angiogenic agents disclosed in Tarara to produce the claimed microspheres useful for embolization having the recited properties.

First, one skilled in the art in the field of embolization would not even look at Bachtsi for any teaching with respect to particles for use in embolization. While it is true that Bachtsi discloses in introductory remarks that hydrogels had been used in the past for drug, enzyme and antibody delivery, the reference does not teach or make obvious the claimed microspheres for use in embolization. These statements, at best, are only an invitation to explore hydrogels in the context of drug delivery. The statement gives no guidance whatsoever as to what to what properties the hydrogels should have or in what fields to explore the use of hydrogels. Further, these statements are in no way specific as to the particular form of the instantly claimed microspheres. Applicants also point out that even though active embolization is a form of embolization that delivers drugs, embolization and

microencapsulation for drug delivery via the gut as disclosed by Bachtsi are significantly different and independent arts. Thus, one of ordinary skill in the art of embolization would not even look to art in the field of gut drug delivery.

Moreover, the mere fact that "hydrogels" existed in the prior art as enzyme, drug, and antibody delivery systems, does not lead one to conclude that the microspheres of Bachtsi should be modified to be sterile, comprise a marking agent or anti-angiogenic agent, and/or would be useful in the field of embolization.

As those skilled in the art are aware, many drug application forms do not require sterile ingredients. For example, pills, ointments, nasal drops, *etc.*, are kept in a clean environment, but do not necessarily have to be sterilized, and tend to be applied or ingested in a non-sterile environment.

Additionally, the subject matter of Bachtsi is concerned with release properties of enzyme-loaded PVA microspheres. The ultimate purpose for studying the enzyme release properties of the microspheres is unclear from Bachtsi. Nowhere do the authors disclose or suggest that theses enzyme-loaded microspheres would be suitable for (1) any pharmaceutical composition, (2) any medical treatment generally, (3) for embolization specifically, and/or (4) any patient population whatsoever, *much less* that the particles should be sterile, comprise a marking agent or anti-angiogenic agent, and/or would be useful in the field of embolization, as recited in the claims.

In an attempt to cure the deficiencies of Bachtsi, the Examiner cites Tarara, which discloses spray drying methods for forming powder compositions for nasal or pulmonary administration, as well as non-pharmaceutical uses for industrial products, such as spray paint.

The Tarara reference, however, does not correct the deficiencies of Bachtsi. Bachtsi does not teach or suggest microspheres useful for embolization comprising sterile crosslinked-PVA microspheres that comprise a marking agent or anti-angiogenic agent. Similarly, Tarara does not disclose, and is not enabling for, microspheres useful for embolization comprising sterile crosslinked-PVA microspheres that comprise a marking agent or anti-angiogenic agent. Tarara discloses spray drying methods for forming powder

compositions for nasal or pulmonary administration. Tarara does not disclose or suggest that the aerosolized powder formulations (*e.g.*, comprising fluorocarbons) would be effective for embolization, nor would one skill in the art expect this.

For at least these reasons, Applicants submit that claims 63-68 are non-obvious over Bachtsi. Accordingly, reconsideration and withdrawal of this ground of rejection is respectfully requested.

D. Boschetti in view of Tarara

The Examiner has also maintained the rejection of claims 1, 4-11, 15-21, 56-60 and 63-68 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Boschetti in view of Tarara (Office Action, page 3; see also prior Office Action dated October 30, 2006, parts 9-10).

Applicants respectfully traverse this ground of rejection.

As discussed above, in *KSR*, the Supreme Court cautioned that "the claimed subject matter may involve more than the simple substitution of one known element for another...." *Id., slip op.* p. 14. Further, "it can be important to *identify a reason* that would have prompted a person of ordinary skill...to combine the elements in the way the claimed new invention does." *Id., slip op.* p. 15 (emphasis added); *see also* USPTO Memorandum ("it remains necessary to identify the reason why a person of ordinary skill in the art would have combined the prior art elements in the manner claimed.").

The instant case involves more than the "simple substitution" of known elements in the prior art. Therefore, the Examiner must provide a reason why one of ordinary skill in the art would combine the teachings of Boschetti and Tarara and somehow arrive at the microspheres of the instant claims. However, the Examiner has provided no basis for the allegation that the instant claims are obvious over Boschetti in view of Tarara, and the Examiner's burden to support a rejection on the grounds of obviousness with explicit, articulate reasoning remains. *KSR, slip op.* p. 14 (*citing In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006); *see also* USPTO Memorandum.

The instant claims are not obvious because the microspheres disclosed in Boschetti in view of Tarara differ from microspheres recited in the instant claims. Furthermore, the scope and content of these references does not provide a reason that would have prompted one of ordinary skill in the art to modify the teachings of Boschetti in view of Tarara to arrive at the methods of the instant claims.

In the prior Office Action dated October 30, 2006, The Examiner cites that Boschetti teaches microspheres useful for embolization comprising hydrophilic acrylic polymers. However, the chemistry of the microspheres of Boschetti is completely different than PVA, and if anything, actually *teach away* from using PVA as the polymers of Boschetti were an alternative to commercially available, irregularly shaped PVA particles (see below).

However, the Examiner correctly acknowledges that Boschetti fails to disclose microspheres comprising a polyvinyl alcohol or microspheres, wherein aldehydes on the microsphere are neutralized.

To supplement the teachings of Boschetti, the Examiner cites Tarara as teaching "that polyvinyl alcohol and acrylic acid polymers are equivalent microsphere structures" but does not provide a citation to such alleged teaching. The Examiner also states that one skilled in the art would be motivated to replace one polymer with another because Tarara discloses that both polymers may be used in the formation of microsphere structures. The Examiner further contends:

> Thus, a skilled practitioner in the art would not expect the overall properties of the microspheres to drastically change by replacing an acrylic polymer with polyvinyl alcohol. In regards to the aldehydes on the microspheres being neutralized, such property would be inherent because the microspheres generated by the prior art and Applicant because since the same microspheres and components thereof are utilized, a skilled practitioner in the art would recognize that a product is inseparable from its properties.

(prior Office Action dated October 30, 2006, page 11).

"In order to rely on a reference as a basis for rejection of an applicant's invention, the reference must either be in the field of applicant's endeavor or, if not, then be reasonably

pertinent to the particular problem with which the inventor was concerned." *In re Oetiker*, 977 F.2d 1443, 1446 (Fed. Cir. 1992).

Applicants again submit that the Examiner has provided no evidence whatsoever nor articulated any explicit reasoning as required by *KSR*, as to why one skilled in the art would be motivated to combine references in completely unrelated fields. That is the Examiner has provided no rationale as to why one skilled in the art of therapeutic embolization would look to Tarara in the field of aerosolized powder drug delivery mechanisms in the first place. Indeed, the art actually taught away from PVA-based microspheres.

The totality of the prior art must be considered, and proceeding contrary to accepted wisdom in the art is evidence of nonobviousness. *In re Hedges,* 783 F.2d 1038 (Fed. Cir. 1986) (Applicant's claimed process for sulfonating diphenyl sulfone at a temperature above 127°C was contrary to accepted wisdom because the prior art as a whole suggested using lower temperatures for optimum results as evidenced by charring, decomposition, or reduced yields at higher temperatures.).

Furthermore, "[k]nown disadvantages in old devices which would naturally discourage search for new inventions may be taken into account in determining obviousness." *United States v. Adams,* 383 U.S. 39, 52 (1966).

At the priority date of the present application, *i.e.*, in October 1998, it is correct that materials useful for embolization, *e.g.*, hydrophilic acrylic-based materials were known (for review, see Flandroy *et al.* "Clinical Applications of Microspheres in Embolization and Chemoembolization: A Comprehensive Review and Perspectives," (1993) *In*: Pharmaceutical Particulate Carriers in Medical Applications, Vol. 61, edited by Rolland, A. New York: Marcel Dekker, Inc., pp. 321-366 at page 329 ("Flandroy"), provided previously in the Response dated April 11, 2007.

However, the majority of particles were made from materials other than PVA, for example, silicone, glass, dextran, polylactide (PLA), poly(2-hydroxyethyl methacrylate) (PHEMA), trisacryl gelatin, and dextran gelatin. *Id.* This was due to the fact that particles composed of other non-PVA material were of greater interest and believed to be easier to obtain compared to PVA particles. However, when it comes to PVA, the standard at the

priority date, and for many years prior, was IVALON, a PVA particle of irregular shape (see, *e.g.*, page 2, line 9 – page 3, line 2 and page 7, line 13 – page 8, line 2 of the specification), which were known to have several disadvantages.

With respect to PVA, Flandroy merely mentions, but does not cite any reference to, spherical PVA (Flandroy, page 329). In fact, the most detailed discussion of PVA particles is of the non-spherical, irregularly shaped IVALON particles (*Id.* at page 328). Flandroy states that the IVALON particles "are not degradable and their immobilization is more proximal than expected" and concludes that "[t]hus, the wrong choice of an embolic material can lead to a proximal occlusion that is as uneffective [sic] as a surgical ligature" (*Id.*) (emphasis added).

The final paragraph of the section on page 330 of Flandroy concludes that, although there are some potential drawbacks, the exemplary non-PVA spherical particles are "suitable" materials for effective occlusions. Thus, after reading Flandroy, one skilled in the art would have no need to look further for other polymeric particles for embolization.

Indeed, Flandroy actually teaches away from the claimed microspheres by (1) teaching that only *non*-PVA spherical particles were suitable for embolization, and (2) PVA was the "wrong choice" for embolic material. As such, a skilled artisan reading Flandroy would have been made aware of the "disadvantages in old devices which would naturally discourage search for new inventions" and would not have been motivated to make the claimed PVA microspheres.

Thus, for at least these reasons, Applicants submit the pending claims are non-obvious over Boschetti, either alone or in combination with Tarara. Accordingly, reconsideration and withdrawal of this ground of rejection is respectfully requested.

III. Conclusion

In view of the foregoing amendments and remarks, Applicants respectfully submit that this application is now in condition for immediate allowance. If the Examiner disagrees, Applicants respectfully request that the Examiner call the undersigned at the number listed below.

A Petition for a One (1) Month Extension of Time, including provisions for the required fee, is submitted herewith, which extends the response period from October 12, 2007 to, and including, November 12, 2007.

A Request for Continued Examination (RCE) Transmittal is also submitted herewith, which authorizes the PTO to deduct the estimated RCE fee of $810.00 to Jones Day Deposit Account No. 50-3013. Applicants believe no other fees are due in connection with this Amendment. However, if there are any fees due, please charge them to Deposit Account 50-3013. Also, please charge any fees underpaid or credit any fees overpaid to the same Deposit Account.

Respectfully submitted,

Date: Oct. 31, 2007

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